REMARKS

Status Summary

The request for continued examination (RCE) filed on September 11, 2006, and the amendment filed on July 10, 2006, have been entered. Claims 56-60 and 62-74 are pending. Claims 1-55 and 61 are canceled. Claims 56-60 and 62-74 under 35 U.S.C. § 103(a) based upon U.S. Patent No. 5,776,456 to Anderson et al. in view of U.S. Patent No. 6,042,826 to Caligiuri et al., and further in view of DeAngelis (1998) *J. Neurooncology* 38:245-252. Claims 56-60 and 62-74 are further rejected under the judicially created doctrine of obviousness-type double patenting over claim 1 of U.S. Patent No. 5,776,456.

Claim 56 is amended as indicated herein above. A declaration by Jane Relton, Ph.D. and pursuant to 37 C.F.R. § 1.132 is also submitted herewith. Reconsideration in view of the amendment, declaration, and following remarks is respectfully requested.

Rejection of Claims Under 35 U.S.C. § 103(a)

Claims 56-60 and 62-74 remain rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,776,456 to Anderson et al. (Anderson) in view of U.S. Patent No. 6,042,826 to Caligiuri et al. (Caligiuri), and further in view of DeAngelis (1998) *J. Neurooncology* 38:245-252 (DeAngelis).

Claim 56-60 and 62-68 are generally directed to a method of treating a central nervous system (CNS) lymphoma comprising the step of administering to a subject diagnosed with the CNS lymphoma, a therapeutically effective amount of an anti-CD20 antibody or fragment thereof, wherein the anti-CD20 antibody is administered intrathecally or intraventricularly, and whereby levels of the anti-CD20 antibody are greater in cerebrospinal fluid (CSF) than in serum. Claims 69-74 are generally directed to a method of treating a central nervous system (CNS) lymphoma comprising the step of administering to a subject diagnosed with said CNS lymphoma a therapeutically effective amount of a radiolabeled anti-CD20 antibody or fragment thereof, wherein the anti-CD20 antibody is administered intrathecally or intraventricularly.

Anderson describes methods for the treatment of B cell lymphoma via administration of anti-CD20 antibodies, while Caligiuri teaches the efficacy of intrathecally administered anti-Fas antibodies against CNS B cell lymphoma. The examiner alleges that it would have been *prima*

facie obvious to one of ordinary skill in the art, at the time the invention was made, to have substituted antibodies known to be efficacious in treating B cell lymphomas, (*i.e.*, the anti-CD20 antibodies of Anderson) for the antibodies known to treat CNS B cell lymphomas, (*i.e.*, the anti-Fas antibodies of Caliguiri) with a reasonable expectation of success. (Official action, item 5, pages 2-5). The examiner supports this contention by stating that anti-Fas antibodies and anti-CD20 antibodies share the same apoptotic mode of action as evidenced by Shan et al., *Blood*, 1998, 91:1644-1652, (Shan I, of record), which was cited in the previously filed declaration pursuant to 37 C.F.R. § 1.132 by Ellen Garber, Ph.D. (Official action, item 5, page 4). The examiner further asserts that even if the modes of action between the two antibodies are different (*i.e.*, that anti-CD20 antibodies require FcR-expressing cells for the induction of apoptosis), applicants have allegedly failed to provide sufficient evidence which demonstrates that the activity of FcR-expressing and NK cells in the CNS was uncertain at the time of the instant invention. (Official action, item 5, page 4).

The examiner alternatively asserts that claims 56-60 and 62-74 are allegedly obvious over the combination of the Anderson and Caliguiri references. The examiner states that because the radiolabeled anti-CD20 antibodies taught by Anderson are encompassed by claims 56-60 and 62-74, a skilled artisan would reasonably expect that such radiolabeled antibodies could be used to effectively treat CNS lymphoma, notwithstanding any uncertainty regarding the activity of FcR expressing NK cells required for anti-CD20 induction of apoptosis. (Official action, item 5, page 4).

The examiner further relies on DeAngelis as teaching the use of known chemotherapeutics for treating neoplasms in the brain. DeAngelis is not discussed further as the examiner states that her reliance on this reference as a secondary teaching is not to support predictive value of treating brain disorders generally (Official action, April 10, 2006, page 4). Based upon the examiner's explanation, it is understood that this reference is cited only against dependent claim 58, which specifies the additional administration of cytarabine and thiotepa or methotrexate and ^{111}In-diethylenetriamine pentaacetic acid.

The foregoing rejection and analysis of the cited references is respectfully traversed as follows.

The examiner bears the burden of presenting a *prima facie* case for obviousness, which requires: (1) some suggestion or motivation, either in the references themselves or in the

knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) the teaching or suggestion of all the claim limitations of the applicant's invention in the combined prior art references; and (3) a reasonable expectation of success. MPEP § 2143. *See also In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). *See also, Ex parte Clapp,* 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). That is, at the time of the invention, one skilled in the art must have believed that the claimed methods could be practiced with a reasonable expectation of success.

In the instant case, applicants respond to the foregoing rejection that, after a review of the cited references, one skilled in the art would not reasonably believe that the presently claimed methods could be practiced with an expectation of achieving therapeutic efficacy. In support thereof, a declaration pursuant to 37 C.F.R. § 1.132 is submitted herewith, which attests that as of the priority date of the instant application, the use of anti-CD20 antibodies for the treatment of CNS lymphomas was unpredictable due to the compromised activity of immune effector cells in the CNS, including natural killer cells and FcR-expressing cells, such as, macrophages, monocytes and dendritic cells. Thus, applicants submit that the examiner has failed to meet the mandated burden.

I. At The Time Of The Invention, Anti-CD20 Antibodies, Unlike Anti-Fas Antibodies, Were Understood To Utilize Fc Receptor (FcR)-Expressing Cells To Enhance Apoptosis

Contrary to the assertions of the examiner, a skilled artisan would not have believed that there was a reasonable chance of success in practicing the claimed invention as of the priority date of the present application because apoptosis induced by anti-CD20 antibodies, unlike apoptosis induced by anti-Fas antibodies, was understood to be enhanced by Fc receptor (FcR)-expressing cells. At the time of the invention, the augmented level of apoptosis induced by anti-CD20 antibodies in the presence of FcR-expressing cells was suggested to contribute to the remission observed in B cell lymphoma patients. In contrast, anti-Fas antibodies were understood to be efficacious in the absence of FcR-expressing cells.

FcR-expressing cells, which are one type of immune effector cells, are capable of mediating various immune effector functions via their interaction with the Fc region of antibodies. (*See, e.g.*, Saalman et al., *Scand. J. Immunol.*, 1998, 47: 37-42 (Saalman); submitted herewith and Fanger et al., *J. Immunol.*, 1997, 3090-3098, (Fanger), submitted herewith). FcR-

expressing cells include dendritic cells, macrophages and monocytes (Shan et al. *Cancer Immunol Immunother*, March 2000, 48:673-683, abstract of record, entire article submitted herewith (Shan II); Saalman; Fanger). These cells mediate effector functions such as antibody-dependent-cellular-cytoxicity (ADCC) or complement dependent cyotoxicity (CDC). Dendritic cells may be further categorized as antigen presenting cells, allowing T-helper cells to become activated in the immune system. (*See*, Pollack et al., *Seminars in Pediatric Neurology,* 2000, 7(2):131-143, Pollack, of record).

In addition to these functions, FcR-expressing cells were also known at the time of the invention to interact with anti-CD20 antibodies to enhance apoptosis in lymphoma cells. For example, Shan I determined that cross-linking of anti-CD20 antibodies by FcR-expressing cells resulted in the enhancement of apoptosis in comparison to the level of apoptosis observed in the absence of FcR-expressing cells, (6.05 to 7.35 +/- 0.81% apoptotic nucleic without FcR-expressing cells vs. 14.10 +/- 0.39% and 25.30 +/- 0.6% with FcR-expressing cells). Shan I, page 1648. Shan I suggested that *in vivo*, FcR-expressing cells may interact with anti-CD20 antibodies to mediate apoptosis that contributes to the remission observed in lymphoma patients treated with anti-CD20 antibodies. (*See also* Shan II *for discussion of* Shan I).

In contrast to the apoptotic activity of anti-CD20 antibodies following cross-linking by FcR-expressing cells, as described by Shan I and Shan II, anti-Fas antibodies induce apoptosis in lymphoma cells in the absence of FcR-expressing cells. In particular, Example 3 of Caliguiri describes experiments to support that primary central nervous system lymphomas expressing significant amounts of cell-surface receptor Fas are susceptible to Fas-mediated cytotoxicity. *See also* Figure 3. Caliguiri states that anti-Fas antibodies were capable of inducing apoptosis by cross-linking of Fas *antigen*. Please note that cross-linking of antigen by anti-Fas antibodies, as described by Caliguiri, is completely distinct from cross-linking of antibodies by FcR-expressing cells. Specifically, cross-linking of antigen by anti-Fas antibodies does not require FcR-expressing cells, and there is no such description of antibody cross-linking in Caliguiri. Accordingly, although both anti-Fas antibodies and anti-CD20 antibodies induce apoptosis in tumor cells, at the time of the invention, anti-CD20 antibodies, unlike anti-Fas antibodies, rely on cross-linking by FcR-expressing cells for efficient induction of apoptosis.

In further support of the foregoing, applicants submit a declaration pursuant to 37 C.F.R. § 1.132 by Jane K. Relton, Ph.D (Relton Declaration). Based on her education and experience in

neurobiology and neuropharmacology, Dr. Relton qualifies as one of skill in the art at the time of the priority date of the instant application. Accordingly, her opinion regarding the expectation of success in performing the claimed invention is relevant to a determination of non-obviousness of the invention.

Dr. Relton attests that, as of the priority date of the instant application, it was known that anti-CD20 antibodies, unlike anti-Fas antibodies, interact with FcR-expressing cells (*e.g.*, dendritic cells, macrophages, or monocytes) to enhance apoptosis. Relton Declaration, ¶¶ 15, 27. Dr. Relton affirms that Shan I and Shan II demonstrate that FcR-expressing cells interact with anti-CD20 antibodies to induce apoptosis, and further suggest that this induction of apoptosis acts in concert with the well known ADCC and CDC activities of anti-CD20 antibodies to mediate remission of B cell lymphoma in anti-CD20 clinical trials. Relton Declaration, ¶¶ 16-21. In contrast to induction of apoptosis using anti-CD20 antibodies, anti-Fas antibodies were observed to induce apoptosis in human B lymphoma cells in the absence of FcR-expressing cells. Relton Declaration, ¶ 27.

II. At The Time Of The Instant Invention, The Activity of Immune Effector Cells In The CNS Was Uncertain

Applicants submit that at the time of the invention, a skilled artisan would not have reasonably expected that anti-CD20 antibodies would be therapeutically efficacious in the CNS because a skilled artisan could not have been certain that FcR-expressing cells (*e.g.*, dendritic cells, macrophages, or monocytes) were active in the CNS. FcR-expressing cells are required for ADCC and CDC activity of anti-CD20 antibodies. *See* Amendment filed January 12, 2006, including Gerber Declaration. As described by Shan II, the successful employment of anti-CD20 antibodies in the clinical treatment of lymphoma may include induction of apoptosis mediated by FcR-expressing cells. *See* Shan II, abstract. Given that immune effector cells are important for all three of the above-described therapeutic mechanisms of action of anti-CD20 antibodies, and that such cells were understood to be substantially compromised or non-existent in the CNS, a skilled artisan would have been uncertain that anti-CD20 antibodies could be therapeutically effective for the treatment of CNS lymphomas. In support of this assertion, applicants direct the examiner to the Relton Declaration submitted herewith.

Initially, Dr. Relton attests that she supports the previously submitted declaration by Dr. Ellen Garber (submitted with the response filed on January 12, 2006). Relton Declaration, ¶ 8. Dr. Garber attested that the CNS is an immunoprivileged site, *i.e.*, a tissue in which immune inhibitory and anti-inflammatory mechanisms physiologically outbalance and counteract immune activity. Because anti-CD20 antibodies depend on immune effector cells, which are compromised in the immunoprivileged environment of the CNS, Dr. Garber stated that the therapeutic efficacy of anti-CD20 antibodies in the treatment of CNS lymphomas has been uncertain. Garber Declaration, ¶¶ 31-35. Dr. Relton concurs with Dr. Garber's statements relating to the uncertainty of the activity of immune effector cells in the CNS, which uncertainty existed as of the priority date of the present application. With respect to the examiner's comments that some of the studies referenced in the Garber Declaration were published subsequent to the priority date of the instant application, Dr. Relton confirms that "the state of the art has not progressed from a state of certainty at the time of the instant invention to a state of uncertainty." Relton Declaration, ¶¶ 9-12.

Specifically, Dr. Relton states that at the time of the present invention, the therapeutic efficacy of anti-CD20 antibodies was known to depend on the induction of cell-mediated immune responses. Relton Declaration, ¶ 13. For example, Anderson describes that immunologically active anti-CD20 antibodies mediate complement dependent cytolysis (CDC) of human B lymphoid cell lines. Anderson also describes that human target cells are lysed through antibody dependent cellular cytotoxicity (ADCC). Relton Declaration, ¶ 14. The cells which mediate CDC and ADCC are immune effector cells such as macrophages and natural killer (NK) cells. Relton Declaration, ¶ 22. Dr. Relton also references Shan I, which describes how FcR-expressing cells are necessary for anti-CD20 antibodies to induce enhanced levels of apoptosis in lymphoma cells. Relton Declaration, ¶¶ 18-19. Accordingly, at the time of the invention, induction of ADCC, CDC, and apoptosis by anti-CD20 antibodies were known to be mediated by immune effector cells. In addition, all three effector cell-mediated mechanisms were believed to contribute to the therapeutic efficacy of anti-CD20 antibodies. Relton Declaration, ¶¶ 20-21.

Dr. Relton further attests that, at the time of the instant invention, it was understood that immune effector cells in the brain were substantially compromised or non-existent. Relton Declaration, ¶ 22. Dr. Relton refers to Pollack, which describes the brain as a challenging

environment in which to initiate an immune response, due in part to the paucity of antigen-presenting cells, such as dendritic cells. Relton Declaration, ¶¶ 23, 25. The dearth of antigen-presenting cells decreases the ability of $CD4^+$ T-helper cells to become activated, which in turn results in reduced development of immune effector cells. Relton Declaration, ¶ 23. Dr. Relton further refers to a summary in Pollack of disappointing results obtained when attempts have been made to enhance immune effector cell activity in the CNS environment. For example, Pollack describes using biological response modifiers to potentially drive the growth and differentiation of immune cells, and/or the activation of immune effector cells in the CNS. Relton Declaration, ¶ 24. These teachings indicate that, at the time of the instant invention, it was well known that the development and activation of immune effector cells in the CNS was limited. Accordingly, as of the priority date of the present application, the use of anti-CD20 antibodies for the treatment of CNS lymphomas was unpredictable due, at least in part, to the uncertainty of immune effector cell activity in the CNS, notwithstanding the success of the same therapies when used systemically for the treatment of non-CNS lymphoma. Relton Declaration, ¶ 28.

Still further, in contrast to the dependence of anti-CD20 antibodies on immune effector cells, Caligiuri demonstrates efficacy of anti-Fas antibodies in the absence of FcR-expressing cells. Accordingly, a person of skill in the art would not reasonably expect that replacing the anti-Fas antibodies of Caligiuri with the anti-CD20 antibodies of Anderson would be useful in the treatment of CNS lymphoma. Relton Declaration, ¶ 28

Based upon the foregoing, applicants have provided sufficient evidence to show that at the time of the instant invention, the activities of immune effector cells, including FcR-expressing cells, in the CNS was uncertain. Because anti-CD20 antibodies require immune effector cells to mediate mechanisms resulting in therapeutic effects (*i.e.*, CDC, ADCC, and/or enhancement of apoptosis), a skilled artisan would not have reasonably expected that anti-CD20 antibodies would be efficacious in the CNS.

III. Radiolabeled Anti-CD20 Antibodies

The examiner alternatively asserts that claims 56-60 and 62-74 are allegedly obvious over the combination of the Anderson and Caliguiri references. The examiner states that because the radiolabeled anti-CD20 antibodies taught by Anderson are encompassed by claims 56-60 and 62-74, a skilled artisan would reasonably expect that such radiolabeled antibodies

could be used to effectively treat CNS lymphoma, notwithstanding any uncertainty regarding the activity of FcR expressing NK cells required for therapeutic efficacy of anti-CD20 antibodies. (Official action, item 5, page 4).

Claim 56 is amended to specify that the anti-CD20 antibody and fragment thereof is unlabeled. Support for the amendment is found throughout the specification as filed, for example, as exemplified by rituximab, which is an unlabeled antibody. In addition, the specification states that antibodies are optionally labeled by conjugation to a cytotoxic agent (*see e.g.*, page 12, lines 5-9, and page 37, line 30 through page 38, line 1). No new matter is entered by way of this amendment. Accordingly, this rejection is rendered moot with respect to independent claim 56 and dependent claims 57, 60, and 62-68, which specify that the anti-CD20 antibody is unlabeled. The amendment is made without prejudice as there are already claims pending encompassing the subject matter excluded from amended claim 56.

Claims 69-74 are generally drawn to a method of treating a central nervous system (CNS) lymphoma comprising the step of administering to a subject diagnosed with said CNS lymphoma a therapeutically effective amount of a radiolabeled anti-CD20 antibody or fragment thereof, wherein the anti-CD20 antibody is administered intrathecally or intraventricularly. The examiner has not met the burden of establishing a *prima facie* case of obviousness with respect to claims 69-74 because the cited references, when considered alone or in combination, fail to motivate practice of the claimed methods. In addition, due to the inherent risks associated with direct administration of agents to CNS, a skilled artisan would not have believed that the claimed methods could be performed with a reasonable chance of success.

Anderson teaches use of radiolabeled anti-CD20 antibodies, but does not teach or suggest administering these antibodies to the CNS. Caligiuri teaches administration of anti-Fas antibodies to the CNS, but does not teach or suggest preparation or administration of radiolabeled antibodies to the CNS. Applicants submit that, at the time of the instant invention, the skilled artisan would not have substituted the radiolabeled anti-CD20 antibodies of Anderson with the unlabeled anti-Fas antibodies of Caligiuri because the skilled artisan would have been aware of the elevated toxicity risks associated with direct administration of therapeutic agents to the CNS. In addition, a skilled artisan could not have been reasonably certain that such a substitution would be therapeutically efficacious such that the claimed methods could be successfully performed.

IV. Summary

Based upon the foregoing, one skilled in the art would not be motivated to replace the anti-Fas antibody in the methods of Caligiuri with the anti-CD20 antibody of Anderson to arrive at the presently claimed invention. As described above, as of the priority date of the present application, a skilled artisan could not have reasonably expected to successfully practice the claimed invention. Thus, the claims are not *prima facie* obvious. Accordingly, applicant respectfully requests that the rejection of claims 56-60 and 62-74 under 35 U.S.C. § 103(a) based on Anderson, Caligiuri, and DeAngelis be withdrawn.

Rejection of Claims Based on Non-Statutory Obviousness-Type Double Patenting

Claims 56-60 and 62-74 remain rejected based on non-statutory obviousness-type double patenting as allegedly unpatentable over claim 1 in U.S. Patent No. 5,776,456 to Anderson et al. (Anderson). The examiner's basis for rejection is the same as that set forth above with respect to 35 U.S.C. § 103(a). Official action, pages 5-6. This rejection is respectfully traversed.

Based upon the arguments set forth above in response to the rejection of claims under 35 U.S.C. § 103(a), which are incorporated herein, applicant believes that the methods of the present disclosure are non-obvious in view of Anderson. As such, applicant also requests that the obviousness-type double patenting rejection be withdrawn.

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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